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Familial risks in testicular cancer as aetiological clues

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Summary

We used the nationwide Swedish Family-Cancer Database to analyse the risk for testicular cancer in offspring through parental and sibling probands. Among 0 to 70-year-old offspring, 4586 patients had testicular cancer. Standardized incidence ratios for familial risk were 3.8-fold when a father and 7.6-fold when a brother had testicular cancer. Testicular cancer was associated with leukaemia, distal colon and kidney cancer, melanoma, connective tissue tumours and lung cancer in families. Non-seminoma was associated with maternal lung cancer but the risk was highest for the late-onset cases, providing no support to the theory of the in utero effect of maternal smoking on the son's risk of testicular cancer. However, the theory cannot be excluded but should be taken up for study when further data are available on maternal smoking. The high familial risk may be the product of shared childhood environment and heritable causes.

Introduction

The aetiology of testicular cancer remains largely unknown, with the exception of undescended testis (cryptorchidism), in utero hormonal exposures and family history (Kumar *et al.*, 1997; Stewart & Kleihues, 2003). It may be discussed as a part of testicular dysgenesis syndrome with a foetal origin (Sharpe & Skakkebaek, 1993; Toppari *et al.*, 1996). Over the last half a century the incidence of testicular cancer has increased two to fourfold in the industrialized countries for unknown reasons (Stewart & Kleihues, 2003; Richiardi *et al.*, 2004). The rapid changes in the incidence and results from immigrant studies indicate environmental factors as a major contribution in the aetiology of testicular cancer (Hemminki & Li, 2002, 2004a). Recently, ecological data from the Nordic countries were used to test the hypothesis of Clemmesen relating maternal smoking at the time of pregnancy to the risk of testicular cancer in the unborn son (Pettersson *et al.*, 2004). The correlations of smoking prevalences among reproductive age women with the risk of testicular cancer in their sons were in agreement with an earlier observation of an increased risk of testicular cancer in sons of women diagnosed with lung cancer (Kaijser *et al.*, 2003). In the present paper we examine familial risks of testicular cancer in the 2004 update of the Swedish Family-Cancer Database, with particular reference to the suggested association of maternal smoking for the unborn son to be later diagnosed with testicular cancer.

Subjects and methods

In the Swedish 'Multigeneration Register', children who were born in Sweden in 1932 and later, are registered with their parents (those pleading parenthood at birth) (Hemminki *et al.*, 2001a). The data on families and cancers have a complete coverage, barring some groups of diseased offspring, which affect those born in the 1930s and who died before 1991. Although this small group of offspring with missing links to parents has negligible effect on the estimates of familial risk (Hemminki & Li, 2003a), we limited the present study to offspring whose parents were known, to eliminate a biased study. This 'Multigeneration Register' was linked by a unique national registration number to the Cancer Registry from 1958 to 2002. Cancer registration is considered to be close to 100% currently (Centre for Epidemiology, 2002).

The site of cancer is registered based on a four-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7). The histological classification of testicular cancers, as present in the Cancer Registry, was used to define seminoma (pathology codes 066) and non-seminoma. From 1993 onwards, ICD-O-2/ICD with histopathological data according to the Systematized Nomenclature of Medicine (SNOMED; http://snomed.org) was used; we refer to this classification as 'SNOMED'. According to this classification, it was possible to distinguish all main histological types of testicular cancer. Standardized incidence ratios (SIRs) were used to measure cancer risks for sons (i.e. offspring) according to occurrence of cancers in their families. Follow-up was started for each offspring at birth, immigration or on 1 January 1990/1958, whichever came latest. Follow-up was terminated on diagnosis of first cancer, death, emigration or the closing date of the study, 31 December 2002. The age of parents were not limited but that of sons were limited to 0–70 years of age. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year age-specific, sex, tumour type, period (10-year bands), socio-economic status (six groups) and residential area (three groups) specific standard incidence rates for all offspring lacking a family history (Esteve *et al.*, 1994). Confidence intervals (95%CI) were calculated assuming a Poisson distribution (Esteve *et al.*, 1994). In addition, 99%CI was calculated. Risks for siblings were calculated using the cohort method as described in Hemminki *et al.* (2001b).

Results

The Family-Cancer Database covered the years 1958–2002 from the Swedish Cancer Registry that included a total of 4586 testicular cancers in sons and 4314 in the fathers. A total of 175 635 cases were recorded in the 0 to 70-year-old offspring population.

The SNOMED histology has been recorded since 1993 and the distribution of histological types of testicular cancer is shown in Table 1. Seminoma comprised 56.2% of all cases with histological specification, followed by teratoma (25.1%), embryonal (13.1%), yolk sac (1.4%) and mixed germ cell tumours (1.4%).

Table 2 presents the risk for testicular cancer in sons depending on the type of cancer in their parents and siblings. At least 10 testicular cancers had to be recorded with any parental cancer for the site to be listed. The SIR for testicular cancer was increased when fathers were diagnosed with testicular cancer (3.78) or when mothers were diagnosed with distal colon cancer (1.97) or with melanoma (1.75). In the case of brothers, only testicular cancer showed an increase (7.55). Kidney cancer in a sister was associated with a risk of testicular cancer (4.19). There was no significant association with lung cancer, although the risk for testicular cancer was above unity in all comparisons. The SIR for testicular cancer was 1.81 ($N = 8$, 95%CI 0.78–3.59) when a sibling was diagnosed with lung cancer (data not shown). However, when the follow-up period was started in 1958, an association of testicular and lung cancers was found for both father and mother probands; the SIRs were 1.22 (114, 1.01–1.47) and 1.39 (54, 1.04–1.81) respectively.

The analysis was reversed in Table 3, which shows SIRs for individuals whose fathers or brothers had testicular cancer. The familial pairs of testicular cancer were the same as in Table 2 but all other comparisons between parents and offspring were unique. When the fathers had testicular cancer, the offspring were at a risk of leukaemia (2.22). Connective tissue tumour in a sibling was associated with testicular cancer in a brother (3.71, $N = 6$, 95%CI 1.33–8.12, data not shown).

In order to find out the association of testicular and lung cancers in more detail, analysis was carried out by testicular cancer histology in two overlapping periods (Table 4). In the longer follow-up period, lung cancer in both father and mother was associated with the son's testicular cancer, yet with low SIRs of 1.22 and 1.38 respectively. The only significant histology-specific increase was for non-seminoma (1.57) in sons whose mothers were diagnosed with lung cancer.

Table 5 shows the SIR for testicular cancer in sons of mothers with lung cancer by diagnostic age. As expected, most seminomas were diagnosed after 25 years of age and most non-seminomas before 36 years of age. The highest risk for both subtypes was observed for sons diagnosed at over 50 years of age; for non-seminoma the SIR was 6.64 and significant. Non-seminoma also appeared to have an early onset component with an SIR of 2.55 (95%CI 0.66–6.59). Most of the late onset cases of non-seminomas were diagnosed in the 1990s and the SNOMED histology assigned the tumours as teratomas, embryonal and mixed germ cell tumours.

Table 1 Testicular cancers according to the SNOMED histology

SNOMED	*N*	%
Seminoma	1516	56.2
Teratoma	677	25.1
Embryonal tumour	354	13.1
Yolk sac tumour	39	1.4
Mixed germ cell tumour	39	1.4
Others with SNOMED	74	2.7
Total	2699	100.0

Discussion

Concordant testicular cancer shows one of the highest familial risks for any cancer (Forman *et al.*, 1992; Heimdal *et al.*, 1996; Westergaard *et al.*, 1996; Moller &

Table 2 SIR for testicular cancer in individuals whose parents or siblings have been diagnosed with any cancer (1990–2002)

	Father only			Mother only			Brother only			Sister only		
Familial site	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	11	0.77	0.38–1.38	1	0.24	0.00–1.35	2	1.32	0.12–4.84			
Stomach	18	0.94	0.56–1.49	10	1.10	0.52–2.03	2	2.24	0.21–8.25	2	3.27	0.31–12.03
Colon	25	0.88	0.57–1.30	29	1.14	0.76–1.63	3	1.71	0.32–5.08	2	1.14	0.11–4.20
Proximal colon	9	0.71	0.32–1.35	8	0.68	0.29–1.34	2	2.50	0.24–9.20	2	2.69	0.25–9.90
Distal colon	13	1.17	0.62–2.01	18	**1.97**	1.17–3.13	1	1.41	0.00–8.09			
Rectum	26	1.32	0.86–1.93	14	1.14	0.62–1.91	1	0.76	0.00–4.36			
Liver	8	0.81	0.35–1.61	5	0.48	0.15–1.13	1	1.52	0.00–8.73			
Pancreas	12	1.03	0.53–1.81	11	1.20	0.59–2.15						
Lung	47	1.13	0.83–1.51	25	1.32	0.86–1.96	4	1.77	0.46–4.56	4	1.85	0.48–4.78
Breast				128	1.17	0.98–1.39				20	0.98	0.60–1.52
Cervix				14	0.74	0.40–1.25				4	0.80	0.21–2.07
Endometrium				23	1.05	0.66–1.57				3	1.34	0.25–3.98
Ovary				23	1.14	0.72–1.71				4	1.11	0.29–2.88
Prostate	97	0.89	0.72–1.09				5	1.28	0.40–3.02			
Testis	12	***3.78***	1.94–6.63				31	***7.55***	5.13–10.73			
Kidney	10	0.64	0.31–1.19	12	1.25	0.64–2.19	2	1.34	0.13–4.92	4	**4.19**	1.09–10.84
Urinary bladder	32	1.07	0.73–1.51	6	0.83	0.30–1.82	2	0.94	0.09–3.45			
Melanoma	20	1.30	0.79–2.01	25	**1.75**	1.13–2.59	2	0.52	0.05–1.91	7	1.35	0.54–2.81
Skin	16	1.03	0.59–1.68	10	1.21	0.58–2.23	1	0.91	0.00–5.22			
Nervous system	21	1.54	0.95–2.35	13	0.91	0.48–1.55	6	1.20	0.43–2.63	4	0.85	0.22–2.21
Thyroid gland	3	1.36	0.26–4.02	7	1.27	0.50–2.64	1	1.56	0.00–8.94	3	1.57	0.30–4.66
Endocrine glands (other)	5	0.96	0.30–2.25	10	0.93	0.44–1.71				3	1.41	0.27–4.18
Non-Hodgkin's lymphoma	19	1.27	0.76–1.99	11	1.10	0.54–1.97	3	1.12	0.21–3.31	4	2.50	0.65–6.45
Myeloma	6	0.91	0.33–2.00	6	1.39	0.50–3.05						
Leukemia	6	0.46	0.16–1.00	6	0.71	0.25–1.55	1	0.36	0.00–2.04	2	0.94	0.09–3.45

95% CI does not include 1.00 (values in bold); 99% CI does not include 1.00 (values in bold italics).

Skakkebaek, 1997; Swerdlow *et al.*, 1997; Hemminki & Li, 2004b; Hemminki *et al.*, 2004). Disappointingly, the efforts to find heritable genes have so far not been successful and the one concern in family and linkage studies may be the unidentified environmental effects that confound heritable effects. A high familial risk between brothers of similar age compared with those with a large age difference may be an indication of environmental contribution to the familial aggregation (Hemminki & Li, 2004a). Strong environmental effects also underlying the changes in testicular cancer incidence in migrants to Sweden. Finns, emigrating from a low-risk area, maintain the Finnish cancer risk but their sons adopt the Swedish risk pattern, although both their parents are Finns. For Danish immigrants, coming from a high-risk area, the trend is opposite (Hemminki & Li, 2002, 2003b). Testicular cancer has also been reported as the site with the highest proportion of childhood shared environmental effects in a family study of all main cancers (Czene *et al.*, 2002). These results suggest that environmental factors during childhood and adolescence impact on the risk of contracting a late-onset testicular cancer (Hemminki & Li, 2004a). Finding these factors would probably help to resolve the riddle of increasing incidence trends.

The higher familial risk for testicular cancer among brothers than father–son pairs may suggest the involvement of a recessive mode of inheritance or an X-linked susceptibility locus in the aetiology of testicular cancer, consistent with the segregation analysis and the gene mapping efforts (Heimdal *et al.*, 1997; Rapley *et al.*, 2000). However, the large difference in SIRs among brothers close in age compared with those further apart is difficult to reconcile without environmental effects, as pointed above. In the present analysis, testicular cancer was associated with a few other types of neoplasia in families. Only melanoma, distal colon cancer, kidney cancer, leukaemia and connective tissue tumours were in excess in families presenting with testicular cancer. The association of melanoma has been observed before, involving both teratoma and seminoma (Hemminki & Li, 2004a).

Scientific data on the possible carcinogenic effects of exposure to smoking during pregnancy, breastfeeding and childhood are scanty. The International Agency for Research on Cancer published recently an authoritative treatise on cancer risks (IARC, 2004). The document

Table 3 SIR for any cancer in individuals whose parents or siblings have been diagnosed with testicular cancer (1990–2002)

	Parent			Sibling		
Offspring site	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	2	1.20	0.11–4.41	3	0.72	0.14–2.13
Stomach	1	0.90	0.00–5.17	4	1.37	0.36–3.53
Colon	3	0.97	0.18–2.87	11	1.35	0.67–2.42
Proximal colon	2	2.49	0.23–9.15	2	2.69	0.25–9.89
Distal colon	1	1.41	0.00–8.09	0		
Rectum	1	0.53	0.00–3.02	5	0.96	0.30–2.27
Liver	1	0.99	0.00–5.68	1	0.39	0.00–2.23
Pancreas	1	0.95	0.00–5.46	3	1.03	0.19–3.04
Lung	5	1.31	0.41–3.09	11	1.03	0.51–1.86
Breast	23	1.28	0.81–1.92	41	0.90	0.65–1.22
Cervix	2	0.69	0.07–2.54	9	1.68	0.76–3.21
Endometrium	3	1.52	0.29–4.49	6	1.09	0.39–2.38
Ovary	2	0.75	0.07–2.75	6	0.97	0.35–2.14
Prostate	3	0.74	0.14–2.18	16	1.26	0.72–2.06
Testis	12	***3.78***	1.94–6.63	31	***7.55***	5.13–10.73
Kidney	1	0.54	0.00–3.10	7	1.67	0.66–3.45
Urinary bladder	2	0.92	0.09–3.38	3	0.51	0.10–1.51
Melanoma	4	0.54	0.14–1.39	16	1.11	0.63–1.81
Skin	2	1.26	0.12–4.62	5	1.30	0.41–3.06
Nervous system	9	1.21	0.55–2.30	12	1.10	0.56–1.92
Thyroid gland	3	1.85	0.35–5.47	5	1.90	0.60–4.47
Endocrine glands (other)	2	0.82	0.08–3.02	6	1.21	0.44–2.66
Non-Hodgkin's lymphoma	7	2.02	0.80–4.19	6	0.88	0.32–1.92
Myeloma	2	3.06	0.29–11.26	0		
Leukemia	9	**2.22**	1.01–4.24	2	0.40	0.04–1.46

95% CI does not include 1.00 (values in bold); 99% CI does not include 1.00 (values in bold italics).

Table 4 SIR for testicular cancer in sons of parents with lung cancer

Son's testicular cancer	Father lung cancer			Mother lung cancer		
	O	SIR	95% CI	O	SIR	95% CI
All (1990–2002)	47	1.13	0.83–1.50	25	1.32	0.85–1.95
Seminoma	27	0.99	0.65–1.45	13	1.09	0.58–1.86
Non-seminoma	20	1.39	0.85–2.15	12	1.73	0.89–3.04
All (1958–2002)	114	**1.22**	1.01–1.47	54	**1.38**	1.04–1.81
Seminoma	62	1.19	0.91–1.52	25	1.18	0.76–1.74
Non-seminoma	52	1.18	0.88–1.55	29	**1.57**	1.05–2.26

95% CI does not include 1.00 (values in bold).

Table 5 SIR for testicular cancer in sons of mothers with lung cancer by age at diagnosis

Son's age at diagnosis	Seminoma			Non-seminoma		
	O	SIR	95% CI	O	SIR	95% CI
0–19	0			4	2.55	0.66–6.59
20–29	5	1.19	0.37–2.79	9	1.00	0.45–1.91
30–39	10	1.03	0.49–1.90	10	1.74	0.83–3.22
40–49	7	1.27	0.50–2.64	3	1.76	0.33–5.22
50–70	3	1.80	0.34–5.33	3	**6.64**	1.25–19.7
0–35	13	1.27	0.67–2.17	20	1.40	0.85–2.16
36–70	12	1.10	0.56–1.92	9	2.19	0.99–4.18
0–25	1	0.61	0.00–3.48	8	1.24	0.53–2.45
26–70	24	1.23	0.79–1.83	21	**1.75**	1.08–2.69
All	25	1.18	0.76–1.74	29	**1.57**	1.05–2.26

Bold type, 95% CI does not include 1.00.

stated that any effects of passive smoking should be reproduced at a higher magnitude in active smokers. The evidence for the risk of childhood cancer caused by maternal smoking was considered inconclusive; similarly, evidence for effects through paternal smoking was inconclusive. An extensive review of childhood cancers has reached an identical conclusion (Little, 1999). However, testicular cancer was not discussed in the above sources. Ecological data from the Nordic countries were recently used to suggest that maternal smoking at the time of pregnancy were related to the risk of testicular cancer in sons (Pettersson *et al.*, 2004). The risk of testicular cancer has been found to be increased in sons of women diagnosed with lung cancer (Kaijser *et al.*, 2003) and also in sons of fathers diagnosed with testicular cancer (Hemminki & Li, 2004a). One obvious problem with this hypothesis is that smoking is not a known cause of testicular cancer among active smokers. We would also assume, if the hypothesis was correct, that the effects of in utero exposure should appear in relatively early-onset cancers, similar to the appearance of vaginal cancers in pubertal and young adult daughters of mothers who were exposed to diethylstilbestrol (Stewart & Kleihues, 2003).

We addressed the question about testicular cancer and in utero exposure and exposure through mother's milk to tobacco products indirectly, using mother's lung cancer as a proxy for her smoking. The lack of smoking data is a disadvantage, but the present design has several merits, including size, high quality (all diagnosis medically verified), nationwide coverage (all parent–offspring covered) and availability of data on potential confounding factors (socio-economic group, period). The SIRs measured between parental lung cancers and any offspring cancers would be elevated if there were genuine heritable causes for cancer susceptibility between two sites. The Swedish Family-Cancer Database has been extensively used to explore familial clusters between cancer sites, including lung and testicular cancers (Li & Hemminki, 2003; Hemminki & Li, 2004a). The present association between lung cancer in mothers and fathers and testicular cancer in sons may be an indication of a heritable susceptibility between the two sites because risks were found for both parents and they were not limited to early-onset cases, which would be assumed if the theory about in utero exposure were correct (Kaijser *et al.*, 2003). The suggested heritable association between testicular and lung cancers was moderately supported by the SIR of 1.81 (0.78–3.59) for sibling pairs affected by these cancers. Yet, more data are needed to prove the suggestive heritable association between testicular and lung cancers.

In summary, testicular cancer shows a strong familial association, which however may be partially environmental. Testicular cancer is also associated with melanoma, distal colon and kidney cancer, leukaemia, connective tissue tumours and lung cancer in families, but it remains to be established whether these associations are causal and whether they are transmitted by heritable or environmental mechanisms. The available evidence does not support the theory linking maternal smoking during pregnancy to the son's testicular cancer. However, the theory cannot be excluded but should be taken up for study when further data are available on maternal smoking.

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Discussion

Dr T Schettler (Newburyport, MA, USA)

Your study confirms that testicular cancer risk is largely influenced by factors in early life, and I wonder if this has implications for all cancers, which are also thought to be influenced by early life factors. The paper by Doll & Peto (*JNCI*, 1981; 66: 1191) in the early 1980s on causes of cancer also referred to immigration data, but they did not consider age at immigration. Does your data suggest that Doll and Peto's conclusions should be changed?

Dr K Hemminki (Heidelberg, Germany)

Our data substantiate the notion that environment is the most important contribution to carcinogenesis, and our findings point to the role of environment at an early stage in life when cell proliferation is maximal and any mistake will result in a clone of abnormal cells.

Dr SJ Assinder (Dunedin, New Zealand)

One of your slides indicated that environmental factors in Sweden had a low risk association with prostate cancer. However, second generation Japanese men in USA have prostate cancer rates which match the host population suggesting that environmental factors have a significant role. Does the prostate cancer rate in Swedish immigrants approach the rate in Swedish men, which would support environmental factors?

Dr K Hemminki

The prostate cancer rate between immigrants born in Sweden and Swedes are identical. In some immigrant groups the rates are lower than those in Swedes. Prostate cancer develops in older men and they may not have been in Sweden long enough for an environmental effect to be noticed.

